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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,483	07/25/2003	Yc Wu	X-0219	4224

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,483	WU ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 7/25/03. There are two claims pending and two under consideration. Claims 1 and 2 are method of making claims. This is the first action on the merits. The application concerns some syntheses of quinazoline compounds.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims parts of 1 and 2, drawn to quinazolines, compounds of formula (I) where $X_1 = X_2 = X_3 = X_4$ = carbon, classified in class 544, subclass 293, among others.

II. Claims parts of 1 and 2, drawn to pyridopyrimidines, compounds of formula (I) where one of X_1, X_2, X_3, or X_4 = nitrogen, classified in class 544, subclass 279.

III. Claims parts of 1 and 2, drawn to Pyrimido[5,4]pyridazines, compounds of formula (I) where $X_1 = X_2$ or $X_3 = X_4$ or $X_2 = X_3$ = nitrogen, classified in class 544, subclass 236.

IV. Claims parts of 1 and 2, drawn to Pyrimido[5,4]pyrimidines, compounds of formula (I) where $X_1 = X_3$ or $X_2 = X_4$ = nitrogen, classified in class 544, subclass 256.

V. Claims parts of 1 and 2, drawn to Pteridines, compounds of formula (I) where $X_1 = X_4$ = nitrogen, classified in class 544, subclass 260, among others.

VI. Claims parts of 1 and 2, drawn to Pyrimido[5,4-d]triazines, compounds of formula (I) where three of X_1, X_2, X_3, or X_4 = nitrogen, classified in class 544, subclass 184.

VII. Claims parts of 1 and 2, drawn to Pyrimido[4,5-e][1,2,3,4]tetrazines, compounds of formula (I) where $X_1 = X_2 = X_3 = X_4$ = nitrogen, classified in class 544, subclass 179.

3. The inventions are distinct, each from the other because of the following reasons: the heterocyclic core of the structure given in claim 1 is the ring bearing variables X_1, X_2, X_3, and X_4. This ring is a mandatory feature and ranges two to six possible heteroatoms. These multiple claimed rings are chemically non-equivalent and are not art-recognized as sharing the same biological properties. Inventions I-VII have acquired a separate status in the art as shown by their different classification, thus the patent search required for Group I is not co-extensive with that required for Groups II-VII. The basic names of these heterocyclic compounds differ, thus the literature search for these various species

will be divergent. Because these inventions are distinct for the reasons given above, restriction for examination purposes as indicated is proper.

Should Applicants traverse the restriction requirement on the grounds that the different core rings are not patentably distinguishable, Applicants should identify such evidence now of record or submit any such evidence that shows the groups to be obvious variants. Such evidence may be used in a rejection under 35 USC 103(a) if the Examiner finds any of the Groups unpatentable over the prior art.

4. During a telephone conversation with Thomas J. Dodd on 5/13/04 a provisional election was made with traverse to prosecute the invention of group I, claims parts of 1 and 2, the quinazoline compounds. Applicant in replying to this Office action must make affirmation of this election.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Objection is made to claims 1 and 2 as containing non-elected subject matter. The claimed syntheses present a variable core for the compounds made. Formula (I) contains compounds drawn to the non-elected inventions.

Title

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: inserting prior to the word "Antifolates", the word, "6-Quinazolinyl-ethyl-benzoyl".

Abstract

8. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. For processes, the type reaction, reagents, and process conditions should be stated, generally illustrated by a single example unless variations are necessary. After restriction, the abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In formula (I), a single bond is drawn between variables X_1 and X_2. From the working examples, was not a double bond intended?

10. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in lines 7-8, claim 1 "or a nitrogen or oxygen protecting group" is indefinite. There are three issues. Firstly, this phrase is not defined in the specification. What is the structure of this claimed protecting group? Secondly, from what is the nitrogen or oxygen to be protected? Are these protecting groups acid stable but removed by base like an acetate group on oxygen? Are these protecting groups base stable but removed by acid like a t-BOC group on nitrogen? Thirdly, are these protecting groups attached through nitrogen and oxygen or directly attached to the pyrimidine ring? A literal reading of the claim is that R_1 and R_2 = -C(O)-OBu^t or $-CH_2C_6H_5$ when the protecting group is BOC or Bzl. Is this intended? The Examiner suggests deleting the phrase.

11. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 12, claim 1, "an amino acid residue" is indefinite. This is not defined in the specification but in the passage spanning line 19, page 6 to line 2, page 7, glutamic acid and aspartic acid are offered as examples. Is this all? Are the twenty natural amino acids that are coded by DNA intended? Are all carboxylic acids with an amino group in the α-position intended? Could this phrase include all organic acid residues containing an amino group somewhere in the molecule, including the acids of sulfur, phosphorus, and boron? How is the residue attached to C(O)-? Must it be through the amino group or can it be attached anywhere?

12. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "carbon" in line 13, claim 1, in the definition of variables X_3 and X_4 leaves two unsatisfied valences in formula (I). The Examiner suggests claiming X_1 and X_2 are "carbon" and X_3 and X_4 are "CH", relying upon formula 1, Scheme 1, page 9 for support.

13. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The phrase in lines 15-17, claim 1 "a starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle" is indefinite for two reasons. Firstly, it purely functional. The phrase does not have an established conventional meaning in organic chemistry that identifies staring materials short of every molecule usable to prepare every possible quinazoline. The phrase "a starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle" does not set forth a means-plus-function element under 35 U.S.C. 112, sixth paragraph. What structures do Applicants intended here? The Examiner suggests using Scheme 2, page 10 to clarify what is meant here.

14. Secondly, does "capable of being cyclized" mean that ability must have been demonstrated in a working example? Or does the mere theoretical possibility of such a cyclization suffice? How plausible must that possibility be? If a similar molecule has been cyclized, does that suffice?

15. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 1, page 24, claim 1 "a reactive moiety" is purely functional. The phrase does not have an established conventional meaning in organic chemistry that identifies staring materials short of

every atom or functional group capable of being further transformed into the 4-ethyl-benzoyl side chain of formula (I). The phrase "a reactive moiety" does not set forth a means-plus-function element under 35 U.S.C. 112, sixth paragraph. What radicals do Applicants intended here? In Scheme 2, page 10 is the "reactive moiety" the nitro group, the amino group, the cyano group, or the "formyl group? Is it all four? There is a diazonium salt intermediate produced in the reaction converting the amino compound to the cyano compound. Is this the "reactive moiety"? The nitro compound in the middle of the first line of scheme 2 conceivably could be made by nitration of an unsubstituted fused benzo ring. The atom lost would be a hydrogen atom. Is hydrogen also included as "a reactive moiety"? The Examiner suggests using Scheme 2, page 10 to clarify what is meant here.

16. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 4, page 24, claim 1 "the 4-substituted moiety" is unclear. Does this mean the "4-substituted aromatic ring fragment" in the previous line, some substituent on the 4-position of the quinazoline ring, or something else? The Examiner suggests replacing "the 4-

substituted moiety" with "4-substituted aromatic ring fragment" if that is what is intended. Better yet, use scheme 2, page 10 to make clear what is being claimed.

17. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in lines 10-11, page 24, claim 2 "the reactive moiety is a nitrogen based leaving group" is unclear. There are three issues. Firstly, since the meaning of "reactive moiety" in unclear, it is hard to understand what is being included or excluded by the new limitation concerning nitrogen. Secondly, does nitrogen based mean the leaving group is only nitrogen, like a diazonium radical? Does nitrogen based also include nitro, amino, or cyano? Thirdly, if cyano is intended, the nitrogen atom of the CN is not found in the product but the carbon atom of the CN is found in the product. Is cyano a leaving group if only part of the radical leaves?

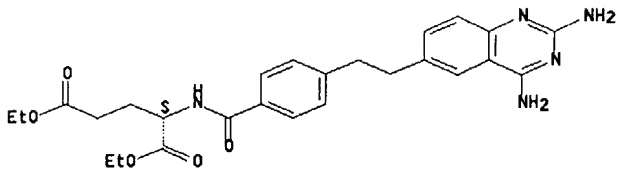
Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan (J. Heterocyclic Chem.). The compound shown below fits formula (I) with $R_1 = R_2 =$

amino, R_3 = hydrogen, X_1-X_4 = carbon, R_4 = C(O)-X, and X = L-Glutamic acid diethyl ester. It has Registry Number 70583-36-7 and is found in column 1, page 542 of the reference. It is compound IX. Synthesis is taught in columns 2, page 542 and column 1, page 543. The reaction sequence is pictured in the reference in the scheme at the bottom of page 541, the second paragraph page 542, and the second



scheme on page 542. The "starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle" is molecule V. Cyclization in a single step is shown in the transformation of V to VIa. Experimental details are found the paragraph spanning both columns of page 542. The "reactive moiety at C6" are radicals R in formulas VIa-VIe. The "4-substituted aromatic ring fragment" is compound VIIIb, shown on page 542 of the reference. The "leaving group at the terminus of "4-substituted aromatic ring fragment" is $(C_6H_5P)_3$.

Four of the radicals R, VIa-VId, contain nitrogen. The transformation of intermediate VIc to VId proceeds through a diazonium salt (N_3^+) intermediate. Thus, claim 2 is anticipated.

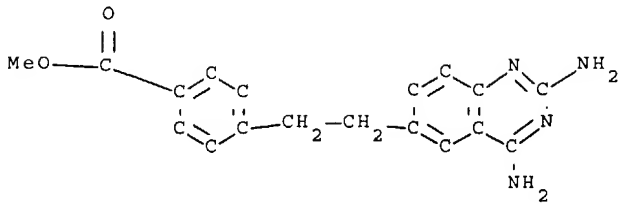
19. The following references are merely cumulative to the art applied above but are made of record, Oatis (Journal of Medicinal Chemistry), Harris (Synlett), and Vaidya (Journal of Medicinal Chemistry).

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nair ('251). The reference teaches the synthesis of the compound shown below. The Applicant claims synthesis of the compound with $R_1 = R_2 =$ amino, $R_3 =$ hydrogen, X_1-$X_4 =$ carbon, $R_4 = C(O)$-X, and X = OCH_3. The reference teaches synthesis of such a compound by a) selecting a starting reagent, b) reacting a reactive moiety at position 6, c) coupling a "4-substituted aromatic ring fragment" having a leaving group, and d) cyclizing the intermediate of step c) in a single step. The process is shown in the reference in Scheme 1, columns 9 and 10. Synthetic details are found



in the passage spanning line 45, column 5 to line 54, column 6. The solid described in line 54, column 6 is the ester pictured above. The difference between the claimed and taught processes is the order of the synthetic steps.

The "starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle" is molecule 3. Cyclization of 3 to a quinazoline in a single step is theoretically possible by reductive guanidation. The "reactive moiety at C6" is the methyl group in formula 3 and the methylene anion generated by sodium methoxide treatment. The "4-substituted aromatic ring fragment" is 4-formylmethylbenzoate. The "leaving group at the terminus of "4-substituted aromatic ring fragment" is either oxygen from the formyl group or the water molecule produced in the condensation reaction.

Merely reversing the order of steps of a multistep process does not impart patentability to the claimed process in the absence of unexpected results, *Cohn et al v. Comr. Pats* 148 USPQ 486, *Ex parte Rubin* 128 USPQ 440, *Ex parte Baril* 124 USPQ 509, and *Ex parte Schwenk* 73 USPQ 85.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/627,485. Although the conflicting claims are not identical, they are not patentably distinct from each other because the two applicants are drawn to the synthesis of the same product. The staring compound

in section a) of copending Application No. 10/627,485 is the same as that shown in Scheme 1, page 9 of the present Application and would constitute a "starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle". The radical CH_2-A_1 shown in part c) of copending Application No. 10/627,485 would appear to be a "reactive moiety". This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

23. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703)

872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK/me